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(71) Applicant *(for all designated States except US)*: SATURNUS AG [LU/LU]; 11, rue Aldringen, L-2960 Luxemburg (LU).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: KONINCKX, Philippe, Robert, Marie, Wilhelmus, Ghislain [BE/BE]; Vuilenbos 2, B-3360 Bierbeek (BE).

(74) Agent: PRINS, Hendrik, Willem; Arnold & Siedsma, Sweelinckplein 1, NL-2517 GK The Hague (NL).

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(54) Title: PREPARATION FOR SUBSTITUTION THERAPY, CONTAINING AT LEAST ONE PROGESTOGEN AND AT LEAST ONE EXTROGEN

(57) Abstract

The invention relates to a preparation for substitution therapy and oral contraception comprising at least one progestogen and at least one estrogen in which the estrogen dose varies with a periodicity such that blood loss is substantially avoided, wherein the periodicity is preferably less than 10 days, more preferably less than 7 days, such as preparations containing the progestogen and/or estrogen in an oral, transdermal, parenteral and/or implantable application form.

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PREPARATION FOR SUBSTITUTION THERAPY, CONTAINING AT LEAST ONE PROGESTOGEN AND AT LEAST ONE ESTROGEN.

The present invention relates to a preparation for substitution therapy and for oral contraception. More particularly the present invention on the one hand relates to relieving the effects which occur because the ovaries decrease or stop production of female hormones, for instance during the menopause. The substitution therapy is mainly intended to induce amenorrhoea with negligible blood loss.

During and after the menopause these effects comprise hot flushes and nocturnal sweating, atrophy of the vagina which can result in sexual difficulties, bone decalcification, increase in heart and blood vessel disorders and psychic symptoms with a causal connection that is usually difficult to demonstrate.

Up to the present different types of substitution therapy have been applied comprising a hormone treatment with one or more oestrogens and one or more progestogens.

According to a first therapy, low doses of oestrogens and progestogens are administered, but such a treatment is ineffective in respect of the decalcification and heart and blood vessel disorders.

In another therapy the natural cycle of oestrogen and progestogen is followed as closely as possible. This treatment inevitably results in menstruation and has the advantage of a reduced risk of cancer of the uterus.

According to yet another therapy only oestrogens are administered in a dose which lies below the threshold for menstrual bleeding. This treatment has the drawback however of an increased risk of cancer of the uterus.

According to a most recently known therapy oestrogens and progestogens are administered continuousl such that the endometrium does not proliferate. This therapy has the drawback however of an unacceptably high incidence of slight, irregular blood loss.

The present invention has for its object to provide a substitution therapy wherein the above described drawbacks occur to a much lesser extent, with the objective of inducing amenorrhoea with negligible blood loss over a long period (many months to years).

On the other hand, the present invention relates to preparations designed for oral contraception with substantially continuous application.

In continuous application of oral contraceptive frequently intermediate bleedings occur. The preparations according to the present invention are designed to induce menstrual bleeding with a regular menstrual bleeding, with an extended cycle or eventually a constant amenorrhoea, but characterized by an optimal (cycle) control and/or by a substantially reduced ocurrence of intermediate bleeding.

EP-A-559 240 discloses preparations for substitution therapy and oral contraception in which the estrogen dose is constant and the progestagen dose is periodically alternated.

However, the improvement in inhibiting endometrium bleeding is minor. Above that, since the use of higher progestagen doses provided better results than lower doses it appears illogical to use periodically varying estrogen doses.

The present invention is based on the finding that suprisingly when using periodically varying estrogen doses the occurence of blood loss and intermediate bleeding is substantially avoided. The estrogen dose is herein oscillated such that estrogen-dominant and progestogen-dominant periods occur alternatingly with a sufficiently short periodicity. This short periodicity in the estrogen dose is necessary to avoid blood loss.

Purely by administering a dose of progestogen or estrogen substantially constant in time and an estrogen or progestogen varying in time between at least two dose levels, it was possible to induce the desired amenorrhoea while no blood loss occurred over a longer period.

The invention therefore relates to a preparation for substitution therapy and for oral contraception comprising at least one progestogen and at least one estrogen in which the

estrogen dose varies with a periodicity such that blood loss is substantially avoided.

It is noted that the preparation is formulated such that a substantially constant blood concentration is obtained for progestogen or estrogen, while the estrogen concentration in the blood varies between two blood concentrations. The periodicity must be sufficiently short and is generally less than 10 days. The periodicity is usually less than 7 days. The periodicity generally lies between 2-9 days, preferably between 2-6 days. It will however be apparent that the periodicity is dependent on the estrogens and progestogens used and the applied doses. Both the periodicity and concentrations of estrogen and progestogen are easy to determine by routine experimentation.

According to an embodiment of the invention the preparation contains a constant progestogen dose, while the estrogen dose oscillates between two levels. This preparation is recommended because there is a greater certainty of avoiding blood loss over a longer period.

According to another embodiment the preparation contains oscillating doses of progestogen and estrogen, in varying ratios however such that blood loss is avoided and amenorrhoea is induced.

Use can be made in general of all known progestogens, such as

progesterone	300-900 mg/day
norethisterone acetate	2-5 mg/day
medroxyprogesterone acetate	1-5 mg/day
d-norgestrel	30-150 µgr/day
desogestrel	30-150 µgr/day
norgestimate	30-150 µgr/day
cyproterone acetate	0.2-2 mg/day,
gestodene	10-150 µg/day
3-ketodesogestrel	10-150 µg/day
drospirenon	0.2-3.0 mg/day

or combinations thereof. It is noted that the preparation can contain one or more progestogens and estrogens.

It will be apparent that the quantity of progestogen and estrogen depends on the person (constitution and age),

the progestogen(s) and estrogen(s), anti-progestogen and anti-estrogen for use and the form of administering same.

The progestogen and estrogen can each be present in an oral, transdermal, parenteral or implantable application form for substitution therapy. The preparation can for instance comprise an application form which contains the progestogen and estrogen, and a second like application form which contains the progestogen and an increased dose of estrogen. The progestogen and estrogen can of course be present in like but separate forms of application or in mutually differing forms of application. The progestogen can for instance be an implantable application form while the oestrogen is administered orally, transdermally or parenterally in a dose which takes account of the required time period according to the invention.

The oral application form to be used comprises tablets, capsules, syrup, solutions. The transdermal forms of application comprise gels, plasters. Strips can for instance be used wherein tablets with progestogen and oestrogen in the desired ratio and periodicity are arranged in time sequence. The parenteral application form comprises injection fluid and the like. The implantable application form comprises for example a known implantable sustained release preparation.

The preparations for oral contraceptive comprise estrogens and progestogens in common form.

Preparations according to the invention were administered over a period of 3-12 months to 40 women in the menopause. By making use of the combination preparations according to the invention a constant amenorrhoea could be obtained in the case of more than 90% of the women, wherein the clinical tolerance was perceived as optimal, wherein the woman did not discern any subjective difference between a fixed or changing oestrogen dose with a periodicity of about one week.

Using the preparations according to the invention as oral contraceptive intermediate bleeding will be substantially reduced.

Example 1

A preparation according to the invention comprised tablets of the type A which contained 10 gamma aethinyl-estradiol, 1 mg estradiol valerianate and 0.5 mg norethisterone, and tablets of the type B which contained 15 gamma instead of 10 gamma aethinyl-estradiol. By alternatingly administering the tablets A and B over a time period of 7 days an amenorrhoea could be induced without blood loss for a very long period of time.

Example 2

A preparation according to the invention contained 1 mg norethisterone or 0.5 mg cyproterone acetate and 2 mg estradiol valerianate. The preparation moreover contained tablets of the type B having 3 mg instead of 2 mg estradiol valerianate. By using the preparation with alternate administering (4-5 days) of the tablets A and B or B and A an amenorrhoea could be induced without blood loss for a longer period of time.

Example 3

A preparation according to the invention comprised tablets of the type A which contained 15 gamma aethinyl-estradiol and 1 mg oestradiol valerianate and 1 mg norethisterone. The preparation moreover contained tablets of the type B having 1.5 mg instead of 1 mg norethisterone. By alternatingly administering the tablets A and B with a periodicity of 4-7 days an amenorrhoea could be induced without blood loss for a very long period of time.

Example 4

A preparation according to the invention for oral contraceptive with optimal cycle control comprises tablets of type A comprising 20 µg aethinyl-estradiol and 75 µg gestoden. The preparation contained tablets of type B comprising 30 µg instead of 20 µg aethinyl-estradiol. Tablets A and B are used in four alternating periods of six days.

Example 5

A preparation according to the invention for oral contraceptive with optimal cycle control comprises tablets of type A comprising 15 µg aethinyl-estradiol and 75 µg gestoden, and tablets of type B comprising 25 µg instead of 15 µg aethinyl-estradiol. Tablets A and B are used in six alternating periods of four days.

In example 4 and 5 only aethinyl-estradiol is used in order to use a estrogen dose which is as low as possible. However, higher estrogen doses may be used. Instead of using a constant progestogen dose fluctuating doses may be use fluctuating simultaneously and/or progressively in view of the varying estrogen dose.

Example 6

A preparation for oral contraceptive according to the invention comprises tablets of type A comprising 20 µg aethinyl-estradiol and 75 µg gestoden, and tablets of type B comprising 30 µg aethinyl-estradiol and 75 µg gestoden and 50 µg onapristone. The tablets A and B are used in four alternating periods of each six days. After four periods the whole cycle is repeated without allowing a free period.

Example 7

A preparation according to the invention for hormone substitution treatment comprises tablets of type A comprising 2 µg estradiol valerianate and 50 µg gestoden. The tablets of type B comprised 3 µg estradiol valerianate and 25-100 µg onapristone. By alternatingly admininstering the tablets A and B over a time period of seven days amennorrhoea could be induced without blood loss for a very long period of time.

It is obvious for a skilled person in the examples in association with intermittently given antiprogestogen or anti-estrogen can be alternated alone or simultaneous with estrogens and/or progestagens. For instance, the antiprogestagen is added in a constant dose to the actual and the above mentioned combinations of estrogens and

progestagens in products for hormone replacement therapy and for contraception.

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CLAIMS

1. Preparation for substitution therapy and for oral contraception comprising at least one progestogen and at least one estrogen in which the estrogen dose varies with a periodicity such that blood loss is substantially avoided.

2. Preparation as claimed in claim 1, wherein the periodicity is less than 10 days, preferably less than 7 days.

3. Preparation as claimed in claim 1 or 2, wherein the periodicity amounts to 2-9 days, preferably 2-6 days.

4. Preparation as claimed in claims 1-3, wherein the dose of progestogen is substantially constant and the dose of oestrogen oscillates.

5. Preparation as claimed in claims 1-3, wherein the dose of progestogen and the dose of estrogen oscillate in such a dose ratio, that blood loss is substantially avoided.

6. Preparation as claimed in claims 1-5, wherein the progestogen comprises

progesterone	300-900 mg/day
norethisterone acetate	0.2-5 mg/day
medroxyprogesterone acetate	1-5 mg/day
d-norgestrel	30-150 µgr/day
desogestrel	30-150 µgr/day
norgestimate	30-150 µgr/day
cyproterone acetate	0.2-2 mg/day,
gestodene	10-150 µg/day
3-ketodesogestrel	10-150 µg/day
drospirenon	0.2-3.0 mg/day

or combinations thereof.

7. Preparation as claimed in claims 1-6, wherein the oestrogen comprises

aethinylestradiol	5-15 gamma/day
oestradiol valerianate	1-4 mg/day
oestradiol	1-2 mg/day
conjugated oestrogen	0.3-1.25 mg/day

oestriol 1-4 mg/day,

or combinations thereof.

8. Preparation as claimed in claims 1-7, comprising anti-progestogen.

9. Preparation as claimed in claim 1-8, comprising anti-estrogen.

10. Preparation as claimed in claims 1-9, containing the progestogen and/or estrogen in an oral, transdermal, parenteral and/or implantable application form.

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INTERNATIONAL SEARCH REPORT

Interr al Application No
PCT/EP 94/02997

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/57 A61K31/565

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 559 240 (JENCAP RESEARCH LIMITED) 8 September 1993 cited in the application see column 12, line 49 - column 14, line 44 ---	1-7,10
A	EP,A,0 275 716 (RUTGERS, THE STATE UNIVERSITY) 27 July 1988 see claims 1,36 ---	1-7,10
A	EP,A,0 279 977 (ALZA CORPORATION) 31 August 1988 see claims ---	1-7,10
A	EP,A,0 346 014 (IMPERIAL CHEMICAL INDUSTRIES PLC) 13 December 1989 see abstract -----	9

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. al Application No
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